## 976 Converting Enzyme and Proteinase Activity in Heart Failure

Tuesday, March 18, 1997, 9:00 a.m.–11:00 a.m.
Anaheim Convention Center, Hall E
Presentation Hour: 9:00 a.m.–10:00 a.m.

### 976-149 Angiotensin II Receptor Antagonist Enhances the Effects of Angiotensin Converting Enzyme Inhibitor in Conscious Pigs with Congestive Heart Failure

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It has been suggested that angiotensin II (AII) is not generated exclusively via the angiotensin converting enzyme (ACE) pathway. The goal of this study was to determine if the addition of AII receptor block enhances the efficacy of an ACE inhibitor (ACEI) during heart failure development. To accomplish this, 5 pigs were instrumented with catheters, left ventricular (LV) pressure gauges, dimension crystals, coronary occluders, aortic flow probes and pacers. Heart failure, induced by serial myocardial infarctions followed by intermittent tachycardiac stress, was manifested by significant decreases in LV dP/dt (−43 ± 8% from 2874 ± 106 mmHg/sec) and cardiac index (−35 ± 5% from 127 ± 7 ml/min/kg) and increases in left atrial pressure (+18 ± 2 mmHg from 4 ± 1 mmHg) and total peripheral resistance (TPR) (+52 ± 12% from 0.72 ± 0.06 units). ACEI (Enalaprilat, 1 mg/kg i.v.) reduced TPR by 14 ± 2 and 10 ± 3% at 15 and 60 min after injection, while fractional shortening and Vcf were slightly increased and LV dP/dt and heart rate were unchanged. ACEI (1 mg/kg) followed by AII block (L-158,809, 1 mg/kg), administered 30 min apart, reduced TPR by 20 ± 4% at 60 min after the initial injection. However, ACEI followed by a 2nd dose of ACEI (1 mg/kg) reduced TPR (−8 ± 3%) less ($p < 0.05$) at 60 min than did ACEI with AII block. Furthermore, higher doses (4 mg/kg) of either ACEI or AII block induced similar peak reductions in TPR (ACEI: −15 ± 4%; AII block: −17 ± 4%). These changes were less than both agents (1 mg/kg each) administered together (−24 ± 4%). These results suggest that in conscious pigs during heart failure, AII receptor block enhances the reduction of peripheral vasoconstriction induced by ACE inhibition.

### 976-150 Association of the Insertion/Deletion Polymorphism of the Angiotensin Converting Enzyme Gene and Angiotensin Converting Enzyme Inhibitor Cough in Patients with Congestive Heart Failure

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Cough limits therapy with angiotensin converting enzyme inhibitor (ACE-I) in heart failure patients. The precise mechanism is unknown, but may be due to lower concentrations of neutral peptidases in the airways. Persons homozygous for the D variant (DD) of the ACE gene, have been shown to have twice the serum ACE activity detected in persons homozygous for I (II). Increased ACE activity may be a compensatory mechanism for decreased neutral peptidases. We hypothesize that heart failure patients with the DD genotype are more susceptible to ACE-I cough compared with patients with the II genotype. PCR was used to identify the polymorphism. Interviews were used to assess individual patient reports of ACE-I induced cough. All patients had ejection fraction ≤ 30% and were receiving an ACE-I for greater than 6 months. Patients complaining of a productive cough, and those with pulmonary edema or infection were excluded. Patients who described their cough as mild, dry, similar to "clearing the throat", or having a "tickling sensation" were categorized with ACE-I induced cough. Patients with the DD genotype had a higher incidence of ACE-I cough compared with patients with the DI or the II genotype ($\chi^2 = 7.7$, $p < 0.025$). Women patients complained of ACE-I cough more frequently than did men (38% vs. 21%, respectively; $\chi^2 = 4.63$, $p < 0.05$). The frequency of the DD genotype was higher in women patients compared with men (75% vs. 39%, $\chi^2 = 20.4$, $p < 0.001$). Heart failure patients with the ACE gene DD genotype appear more susceptible to ACE-I cough compared with DI or II patients. ACE genotype may explain in part the increased frequency of ACE-I cough reported by women patients.

### 976-151 Matrix Metalloproteinase Alterations in the Canine Atrium and Ventricle During Rapid Ventricular Pacing

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Rapid canine ventricular pacing produces remarkable cardiac structural remodelling resulting in atrial but not ventricular hypertrophy. We evaluated by zymography the role of matrix metalloproteinases (MMPs) in 24 dogs; 9 controls, 8 paced 1 week, and 7 paced 3 weeks. Hypertrophy was assessed by LA appendage (LAA) weight at post mortem. LV mass and LA and LV cross-sectional areas (CSA) were acquired by echo. Data x ± SD for left atrium (LA), left ventricle (LV) is shown in the table. This confirms atrial but not ventricular hypertrophy despite similar proportionate increases in CSA. LA hypertrophy is accompanied by elevated MMP2 activity by week 1 and elevated presumed, ie. kDa 52, stromelysin ("MMP3") by 3 weeks of pacing. In contrast only MMP9 activity by the 3rd week is significantly increased in the non-hypertrophied LV (*$p < 0.05$).

| | | Control | 1-week paced | 3-week paced |
|---|---|---|---|---|
| Heart | wt (g) | 198.5 ± 45 | 191.9 ± 32 | 178.6 ± 34 |
| LAA | LAA/heart | 0.010 ± 0.004 | – | 0.020 ± 0.006* |
| | CSA ($cm^2$) | 8.22 ± 1.18 | 12.66 ± 1.56* | 15.21 ± 1.50* |
| | MMP2 | 1.05 ± 0.27 | 1.51 ± 0.39* | 1.30 ± 0.30 |
| | "MMP3" | 0.33 ± 0.31 | 0.90 ± 0.56 | 1.10 ± 0.51* |
| | MMP9 | 25.78 ± 5.21 | 31.99 ± 13.02 | 27.09 ± 12.12 |
| LV | mass (g) | 88.91 ± 12.79 | 101.33 ± 15.84 | 102.60 ± 24.43 |
| | CSA ($cm^2$) | 14.46 ± 2.29 | 19.19 ± 2.50* | 21.41 ± 3.71* |
| | MMP2 | 0.63 ± 0.34 | 0.92 ± 0.43 | 1.00 ± 0.35 |
| | "MMP3" | 0.69 ± 0.41 | 1.02 ± 0.38 | 1.05 ± 0.59 |
| | MMP9 | 22.91 ± 7.20 | 25.18 ± 5.02 | 33.36 ± 7.62* |

We conclude that the differential hypertrophic response in atria vs. ventricle may relate to activation of MMPs directed towards elements of basement membrane and extracellular matrix.

### 976-152 Deleterious Actions of Dietary Sodium Restriction Upon the Progression of Experimental Congestive Heart Failure

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The modulation of dietary sodium upon the progression of congestive heart failure (CHF) remains poorly defined. We tested the hypothesis that dietary sodium restriction in contrast to excess results in premature activation of vasoconstrictors and growth-promoting humoral factors during the progression to overt CHF. We studied the effects of low sodium (10 mEq/day, n = 6), normal sodium (55 mEq/day, n = 6), and high sodium (250 mEq/day, n = 6) diet in a conscious canine model of tachycardia-induced CHF in which dogs were paced at an initial rate of 180 bpm and progressively increased to 240 bpm to produce overt CHF. All groups demonstrated similar decreases in MAP and CO ($p < 0.05$) and increases in RAP, PAP, and PCWP ($p < 0.05$). Dietary sodium restriction resulted in early activation of plasma renin activity (5.2 ± 1 vs 2.3 ± 1.7 ng/ml/hr, $p < 0.05$), aldosterone (18 ± 5.0 vs 2.7 ± 1.2 pg/dl, $p < 0.05$) norepinephrine (317 ± 53 vs 204 ± 47 pg/ml, $p < 0.05$), and epinephrine (324 ± 76 vs 96 ± 22 pg/ml, $p < 0.05$) in ALVD which persisted during progression of CHF. This early and sustained humoral activation was associated with a greater decreases in ejection fraction (37.1 ± 2.9 vs 25 ± 1.9%, $p < 0.05$) despite similar cardiac filling pressures and a decreased left ventricular end diastolic diameter (44.0 ± 1.2 vs 49.6 ± 1.3 mm $p < 0.05$) in overt CHF. This study demonstrates that dietary sodium restriction accelerates activation of vasoconstrictor and mitogenic humoral factors leading to a greater reduction in left ventricular systolic function while dietary sodium excess attenuates neurohumoral activation in the during the evolution of experimental heart failure.

### 976-153 Differential Regulation of Cardiac Angiotensin Converting Enzyme (ACE) Binding Sites and $AT_1$ Receptor Density in Primary Pulmonary Hypertension (PPH)

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Because isolated failure of the right ventricle (RV) occurs in PPH we tested the hypothesis that ACE binding sites would be increased and angiotensin II receptors (ATRs) decreased only in the RV of PPH hearts. We used $^3$H-ramiprilat to quantify ACE binding sites and saralasin ($^{125}$I-[Sar$^1$, Ile$^8$]-Ang II) to measure ATR density in left and right ventricles of PPH hearts